Full Title: Short-term outcome of first episode diagnosis of substance induced psychotic disorder in a large UK cohort

Running title: First episode substance induced psychosis outcome

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Abstract

Objective

The incidence and outcome of first episode Substance Induced Psychotic Disorder (SIPD) is unclear. The study aimed to compare the 1-year outcomes of those given a SIPD diagnosis by clinicians compared to other psychosis diagnoses in a first episode cohort.

Method

Data was from a large (n=1027) cohort of First Episode Psychosis (FEP) patients admitted to early intervention services in the UK (National EDEN). Diagnosis, including that of SIPD, was made by treating psychiatrists at baseline using ICD10 criteria. Details on symptoms, functioning, quality of life, relapse and recovery was available at baseline and 12 months.

Results

There were 67 cases of SIPD (6.5% of the cohort). At baseline SIPD patients were no different to other psychoses on symptoms, functioning and quality of life. At 12 months there was no difference in SIPD and other psychoses on functioning, quality of life or relapse and recovery rates. Levels of psychotic and general symptomatology were similar but depressive symptoms were higher in the SIPD group.

Conclusions

FEP patients with a diagnosis of SIPD do not appear to have better outcomes that those with other primary psychotic diagnoses. The higher levels of depressive symptoms may be a specific marker in these patients.

Keywords: First episode psychosis; Substance induced psychotic disorders; Outcome; Cohort study

Significant outcomes

- There were no differences in baseline symptoms and functioning levels between those with a clinician diagnosis of substance induced psychotic disorder (SIPD) and other psychosis diagnoses in a large first episode psychosis cohort.
- At 12 months follow-up there were higher levels of depressive symptoms in those with SIPD compared to those with other psychosis diagnoses.
- There were no differences in other outcomes between the SIPD and other psychosis groups at 12 month follow-up including other symptomatic or functional outcomes, rates of relapse and recovery.

Limitations

- The diagnosis of SIPD was made by clinicians using ICD 10 criteria and not using a specific validated diagnostic tool. The diagnosis was only possible if patients disclosed their substance use.
- The numbers of individuals with SIPD was relatively low reducing the ability to identify small differences in outcome.
- Treatment offered to the two diagnostic groups over the 12 month period were not fully characterized.

Introduction

Since the early 1990's the Early Intervention in Psychosis (EIP) movement has led to services reconfiguration in the UK and worldwide with specialist Early Intervention (EI) teams developed which aim to treat emerging psychotic disorder and improve functional outcomes (1). The early intervention paradigm has assumed a symptom "threshold" (in terms of frequency and intensity) approach for what constitutes psychosis (2) that encompasses a range of disorders, from schizophrenia spectrum disorders, mood disorders with psychosis, and substance induced psychotic disorder (SIPD). However, there is debate on whether the treatment of persistent psychotic symptoms assumed to be in the context of other primary disorders should be the remit of EI teams (3).

One particular area of debate is whether SIPD should be treated in the same manner as other psychoses within these services, or even referred to these services in the first place (3). This is predicated on the widespread assumption that outcomes for SIPD are different to other psychotic disorders. The current International Classification of Diseases ICD10 (4) defines SIPD as "a cluster of psychotic phenomena that occur during or following psychoactive substance use but that are not explained on the basis of acute intoxication alone and do not form part of a withdrawal state" although the category of residual and late-onset psychotic disorder would also be considered here, though often presenting at a later age (ICD 10). The prevalence of SIPD has been estimated to be 1.9/100,000 person years, which is around 5% of all case of psychosis (5). However, as lifetime prevalence of substance use in first episode patients is high, as is the levels of substance use at presentation to services (6), diagnostic difficulties are common. Studies have reported the diagnosis of SIPD is relatively unstable and

there is a considerable “progression” to more schizophreniform diagnoses (7-9). A follow-up sample with a primary psychotic disorder plus substance use and those with SIPD revealed that they also receive different treatment approaches such as differential prescribing of antipsychotic medication (10). Other studies have reported that SIPD patients are less likely to be hospitalized, less likely to be started on antipsychotics and referred to psychiatry that those with primary psychotic disorder (11). Clinically, this is usually justified on the basis of an assumption that SIPD has a good short-term prognosis, will be short lived and self-limiting with ultimate resolution being provided by abstinence from the substance. Good quality evidence for these widespread clinical assumptions is however lacking (12) and the current evidence is conflicting with some studies suggesting there is a good outcome (10) and other reporting high rates of psychotic relapse in SIPD (8).

Given these findings of diagnostic instability and uncertain outcomes there is a lack of clarity on the most suitable care pathway that should be instituted for these patients presenting with a first episode psychosis (FEP). In a critical review of SIPD, the authors identified only 18 articles specifically focusing on delineating the clinical characteristics or outcomes and only 1 that reported 1 year follow up data (12). There have been no studies to our knowledge that have investigated both symptomatic and functional outcomes in incident cases of SIPD compared to other diagnostic groups. This information would have considerable implications for treatment and follow-up of these patients. For example, should the outcomes be substantially better, there may be an argument for shorter or less intensive treatment pathways.

Aims of the study

The study aimed to investigate the 12-month outcome of first episode psychosis patients in a large UK FEP cohort who were diagnosed with a SIPD compared to other psychotic disorders. There were two hypotheses: 1) functional outcomes in SIPD would be similar to other psychotic disorders 2) symptomatic outcomes would be better in the SIPD group than for other psychotic disorders and they would experience fewer relapses.

Methods and materials

Sample

The data was taken from the national EDEN database (13) of 1027 FEP cases admitted to EI services between August 2005 to April 2009 from five geographical sites across England: Birmingham, Cornwall, Cambridge, Norwich and Lancashire (13). National EDEN was a study of outcomes in UK Early Intervention Services. The UK Department of Health guidance for inclusion into these services is broad and requires only that patients are 'aged between 14 and 35 with a first presentation of psychotic symptoms' (14). Data was recorded throughout the treatment with the service up to 12 months. For further details of the sample see Birchwood et al (13). The treatment pathway in EI services is determined by the UK National Institute for Health and Care Excellent guideline for Schizophrenia and Psychosis (15) and the national IRIS Early Psychosis guidelines (16). The standard length of treatment for any patient accepted into an EI service in the UK is 3 years. Team structure for EI teams in the UK has previously been recommended by the Department of Health (14).

Ethical approval for the study was given by Suffolk Local Research Ethics Committee, UK.

Diagnostic groups

Research assistants recorded ICD 10 diagnoses made by the treating consultant at entry to the service from the clinical files. The OPerational CRITeria (OPCRIT) diagnostic system was also used in the cohort but OPCRIT does not give a diagnosis of SIPD as one of the outputs (17). There was a number of diagnoses made including substance induced psychosis, schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder and unspecified psychosis. Unspecified psychosis was the largest diagnostic group, likely due to these clinical diagnoses being made at first contact with services when duration of symptoms may be less clear, symptoms fluid and a generic diagnosis of "first episode psychosis" (or unspecified psychosis) common practice in UK early psychosis services. Those with a diagnosis of SIPD were compared to the overall group of other psychosis diagnoses.

Outcome measures

A number of symptom and functional outcomes were available at 12-month follow-up as well as at baseline in the cohort.

<u>i) Symptoms</u>

The following symptom scales were available at baseline and 12 months: Positive and Negative Syndrome Scale (PANSS), yielding total, general, negative and positive

symptoms scores (18)); The Young Mania Rating scale (YMRS) (19); The Calgary Depression Scale (20); The Global Assessment of Functioning (GAF) scale (21) (symptoms indicated by GAF total, GAF symptoms).

ii) Functioning and quality of life measures

The following functioning and quality of life measures were used that were collected at baseline and 12 months: The Global Assessment of Functioning (GAF) scale (21) (functioning indicated by GAF total, GAF disability); EuroQual 5 Dimensions Questionnaire (EQ-5D) (22) (using the overall score and the health thermometer score); Time use survey (23).

iii) Relapse and recovery

Using standard international definitions of relapse and recovery from the Bebbington et al method (24). This was summated at 12 months to give rates for both of these outcomes at this time point.

Analyses

The baseline characteristics of those with a diagnosis of SIPD with the group with other psychosis diagnoses were compared statistically using analysis of variance and chi-squared tests. A regression model was used to investigate outcome by diagnostic group, with the individual outcome of interest at 12 months as the independent variable and diagnostic group as the dependent variable. Covariates in an adjusted model included age, gender, ethnicity, Duration of Untreated Psychosis (DUP) and baseline outcome scores. Analyses were performed using SPSS version 22.

Results

Of the 1027 cases in the National EDEN database, there were 954 (92.9%) individuals with a recorded clinician diagnosis at baseline (entry to the service). Of these 954 individuals, 685 (66.7%) had a diagnosis of unspecified psychosis, 136 (13.2%) schizophrenia, 50 (4.9%) bipolar disorder, 16 (1.6%) schizoaffective disorder and 67 (6.5%) SIPD. The patients used a multitude of substances and the rate of previous illicit substance use was high in the total sample (65.2%). However, when investigating the primary substance used in both the SIPD and other psychosis groups this was predominantly cannabis (93.7% in the other psychosis group and 93.8% in the SIPD group). The SIPD group were far more likely to use more than one substance, for example the percentage of the SIPD group reporting use of a second substance was 75.6% compared to 37.8% in the other psychoses group. However, it was not specified which, if any of the substances used, was implicated as the primary cause of the SIPD.

Baseline characteristics of the sample

The baseline characteristics of the sample are presented in Table 1. There were no significant differences in demographic characteristics between SIPD and the other psychoses group (see Table 1). There were there also no significant differences between the two diagnostic groups at baseline on symptoms, functioning and quality of life (see Table 2) with the only (expected) difference being the lifetime use of substances.

Insert Table 1 around here

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Differences at 12 months outcome

At 12 months post diagnosis there were few differences between the SIPD group and the other psychosis group. Scores on functioning, quality of life and rates of relapse and recovery were not different between the two groups. This was the case for both the unadjusted analyses and the analysis adjusted for age, gender, ethnicity, DUP and baseline score. The only significant difference on symptoms was that the SIPD group scored higher on the Calgary Depression Scale (both unadjusted and adjusted for age, gender, ethnicity, DUP and baseline Calgary score) (see Table 3). Rates of substance use in the 3 months prior to follow-up were still significantly higher in the SIPD group than the other psychosis group 55.1% in the SIPD group and 25.2% in the other psychosis group, $p<0.001$).

Insert Table 3 around here

Discussion

Summary of results

In this study the outcome of the clinician diagnosis of SIPD compared to other psychotic diagnoses was compared using data from a large FEP cohort. The study found that functional outcomes for individuals with SIPD were not different to those

with other primary psychotic disorders. This supported the first hypothesis which was functional outcomes in SIPD would be similar to other psychotic disorders. The functional and quality of life outcomes were improved for all disorders but remain relatively low for SIPD despite 12 months of treatment in an EI service. However, contrary to the second hypothesis, levels of relapse and recovery were similar in the SIPD and other psychosis group. The only difference on symptomatic outcome was that the SIPD group had higher levels of depression at 12 months.

Comparison to other research

There have been few other research studies comparing the outcome of first episode SIPD to other psychotic disorders. In a critical review of SIPD, the authors identified only 18 articles specifically focusing on delineating the clinical characteristics or outcomes and only 1 that reported 1 year follow up data (12). A report from the US highlighted differences between SIPD and those with primary psychosis and concurrent substance use at baseline (25). In terms of symptoms they reported that the SIPD group had more visual hallucinations but that the primary psychosis group had higher scores in the PANNS negative, positive and general scales as well as lower insight scores. Remission rates were also higher in the SIPD group (26). This was not the case in this cohort. There are some differences in the samples, which might explain these differences. Although the above sample was first episode sample, patients were recruited from emergency departments in the US whereas our sample was from all patients accepted into UK EI services, which is the modal pathway for first episode treatment in the UK. It may also be that the treatments provided to these diagnostic groups are different in the US and the UK.

Others have suggested that there may be distinct psychopathological differences between SIPD and primary psychosis, including levels of affective symptoms (27) and this might help to distinguish the diagnosis of SIPD from primary psychotic disorders with substance use. Related to this is the suggestion of high rates of progression to an affective disorder in this group as well as a psychotic disorder (28). The current study also found that affective symptoms, especially depressive symptoms at follow-up, were different in the two groups. At present we are unsure if this reflects different treatment pathways, worse adherence to treatment in this group, the consequences of continued significant substance use, or an affective marker in these patients, but this would warrant further study. Others have found different factors that are able to predict the diagnosis of SIPD versus a primary psychotic disorder including family history of psychosis, trauma history and current cannabis dependence (29) and distinct differences in symptom profile at baseline (30). There may also be some differences due to the type of substance inducing the psychotic disorder (31). There is also work investigating whether there are neurobiological differences to distinguish these two diagnostic groups (32). We found no differences other than prior history of substance use to distinguish these groups at baseline in our cohort.

Strengths and limitations

The numbers in the overall National EDEN database are large and it represents the largest cohort of FEP patients receiving treatment available currently. However, the numbers of individuals with SIPD are still relatively low (n=67). Given the relatively

small numbers in the SIPD group estimation was conducted with relatively low precision, especially with regard to the difference in symptomatic outcome and relapse. However, there were multiple symptom measures available, the confidence intervals for most of the symptom measures in the SIPD group were relatively narrow and the finding of increased levels of depression in the SIPD was supported by extant literature. There were some missing data on both symptoms and functioning for both groups but this was relatively modest. Hence a missing data analysis was not performed. The diagnosis of SIPD was made by the consultant psychiatrist in the EI service using ICD 10 criteria and recorded by the researcher but the diagnosis was not made using a structured interview such as the SCAN (33). Therefore, our results essentially reflect the outcome of what psychiatrists believe represents a diagnosis of SIPD at entry to an EI service. Whilst this might indicate a reduced reliability of diagnosis in research terms, our findings on the other hand do strongly represent routine clinical practice and have considerable face validity and clinical relevance. OPCRIT (15) diagnoses were available for this cohort, but OPCRIT does not give a diagnosis of SIPD as an output. The diagnosis of SIPD has been shown to have reasonable validity, although with some caveats (12), and does encompass psychosis induced by a variety of psychoactive substances, with some possible differences in presentation between these (34). The rate of SIPD diagnosis in the cohort as a whole (6.5%) is similar to the published incidence rates for all psychotic disorders versus SIPD's (5). However, further research is needed in first episode psychosis samples using validated and reliable diagnostic tools to substantiate these findings. In this sample we do have a high number of non-specific diagnoses (unspecified psychosis) made by clinicians likely due to the widespread practice of giving a non specific psychosis diagnosis on entry to EI services but some clinicians have made the

decision on the diagnosis of SIPD early in the course. We are not clear whether this reflects a degree of certainty from the clinician or a tendency to attribute an aetiological (and possibly less stigmatizing) cause for the presentation. We were unable to compare the specific treatments that the diagnostic groups received. The treatment offered by EI services in the UK is a broadly consistent 3-year program, following NICE guidance (15), although specifically tailored by the individual patient formulation and to some extent the diagnosis. Lastly, we are aware that we have investigated the relatively short-term outcome of these patients and there is a need to consider the long-term outcome further.

Clinical implications

The results have implications for both those who refer to EI services such as emergency departments, acute services and other community psychiatric teams and for the treatment of patients with SIPD within these services. EI services have debated whether SIPD should be treated within their teams and at times these patients anecdotally have not been referred to EI services (3). The results from this study would suggest that outcomes of patients given this diagnosis by psychiatrists are not significantly more favourable, in fact they possibly have poorer affective outcomes. In this respect, they are in need of a service based on both symptomatic and functional outcomes. As such this may argue for a more assertive treatment approach for this group and challenge clinical strategy based on the view that long-term follow-up is not required. The incidence of SIPD reported in a recent meta-analysis is 1.9/100,000 person years is not insignificant (5). The literature on the rates of development

schizophreniform disorder in those with an initial diagnosis of SIPD would suggest that EI services are best placed to provide this service, especially if the teams have specific training in treatment of dual diagnosis. Having said this, the predictors of poor outcome in SIPD are relatively understudied and knowledge of these predictors would help to "stream" treatment approaches within services. Our work suggests that psychosis linked to substance misuse has poor outcomes, whether the substance misuse is a seen as 'comorbidity', or a risk factor, or deemed to have triggered the psychosis. The treatment of depressive symptoms needs further emphasis, especially as we know that substance use is a risk factor for suicide in FEP patients (35).

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Conflicts of Interest

None

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Table 1: Baseline demographics and substance use of the sample by diagnostic group

	Other Psychoses*	Substance Induced Psychotic Disorder *	Total*	P value
Age at onset (N=929)	21.3 (5.0)	20.7 (4.4)	21.3 (5.0)	0.354
Gender (N= 954), male (%)	608 (68.5%)	50 (75.8%)	658 (69.0%)	0.135
DUP (N=940), Mean (SD)	328.3 (670.5)	154.7 (243.5)	316.1 (651.2)	0.037
Educational level/Qualifications (N=939)				
None	212 (24.3%)	18 (27.3%)	230 (24.5%)	0.511
Basic (GCSE/NVQ ½)	339 (38.8%)	30 (45.5%)	368 (39.2%)	
Advanced (A level/BTEC/NVQ3)	230 (26.3%)	15 (22.7%)	245 (26.1%)	
Degree/HND/NVQ 4+	88 (10.1%)	3 (4.5%)	91 (9.7%)	
Special needs educational qualifications	5 (0.6%)	0 (0%)	5 (0.5%)	
Ethnicity (N=954)				
Asian	128 (14.4%)	11 (16.4%)	139 (14.6%)	0.416
Black	58 (6.5%)	1 (1.5%)	59 (6.2%)	
Caucasian	660 (74.3%)	51 (76.1%)	710 (74.4%)	
Mixed	35 (3.9%)	4 (6.0%)	39 (4.1%)	
Other	7 (0.8%)	0 (0%)	7 (0.7%)	
Living circumstances (N=951)				
Alone	118 (13.3%)	3 (4.5%)	121 (12.7%)	0.194
With parents/guardians	554 (62.6%)	47 (70.1%)	601 (63.2%)	
With partner	94 (10.6%)	6 (9.0%)	100 (10.5%)	
Other	119 (13.4%)	11 (16.4%)	129 (13.6%)	
Occupational circumstances (N=949)				
Working (paid)	161 (18.2%)	11 (16.7%)	172 (18.1%)	0.745
Working (voluntary)	9 (1.0%)	0 (0.0%)	9 (0.9%)	
Unemployed	511 (57.8%)	43 (65.2%)	553 (58.3%)	
Homemaker	20 (2.3%)	2 (3.0%)	22 (2.3%)	
Student	172 (19.5%)	10 (15.2%)	182 (19.2%)	
Other	11 (1.2%)	0 (0.0%)	11 (1.2%)	

* N for SIPD = 67, for other psychosis = 887 and total = 954, number vary slightly by individual variable

Footnote: DUP=Duration of Untreated Psychosis; GCSE= General Certificate of Secondary Education; NVQ=National Vocational Qualification; BTEC= Business and Technology Educational Council; HND=Higher National Diploma

Table 2: Baseline symptoms and functioning scores by diagnostic group

		Other Psychoses*	Substance Induced Psychotic disorder*	Total*	P value
GAF total	N Mean score (SD)	837 50.1 (17.1)	60 52.9 (16.7)	897 50.3 (17.0)	0.188
GAF symptoms	N Mean score (SD)	827 51.1 (16.6)	61 52.5 (17.3)	888 51.2 (16.6)	0.488
GAF disability	N Mean score (SD)	825 52.9 (15.2)	61 53.7 (15.6)	886 52.9 (15.2)	0.577
Calgary Depression Scale	N Mean score (SD)	832 6.5 (5.4)	58 5.6 (4.7)	890 6.4 (5.4)	0.250
YMRS	N Mean score (SD)	832 6.0 (7.3)	56 6.5(7.5)	888 6.1(7.3)	0.658
Insight scale	N Mean score (SD)	616 7.75 (3.0)	51 7.90 (3.0)	667 7.76 (3.0)	0.731
Lifetime substance use	Yes No	557(64.6%) 305 (35.4%)	66 (98.5%) 1 (0.3%)	622 (67.0%) 306 (33.0%)	 <0.001
PANSS positive	N Mean score (SD)	827 15.4(6.0)	61 15.6 (6.7)	888 15.4 (6.1)	0.843
PANSS negative	N Mean score (SD)	806 15.0 (6.4)	60 14.2 (7.8)	866 14.9 (6.5)	0.349
PANSS general	N Mean score (SD)	817 33.2 (10.0)	58 31.5 (9.5)	875 33.1 (10.0)	0.258
PANSS total	N Mean score (SD)	798 63.3 (18.7)	58 61.7 (17.5)	856 63.2 (18.8)	0.527
EQ-5D health thermometer	N Mean score (SD)	723 60.6 (21.9)	53 62.4 (21.9)	776 60.7 (21.9)	0.555
EQ – 5D total score	N Mean score (SD)	768 6.9 (1.7)	59 6.9 (1.6)	827 6.9 (1.7)	0.937

*overall N for SIPD = 67, for other psychosis = 887 and total = 954, number vary slightly by individual symptom outcome

Footnote: GAF= Global Assessment of Functioning scale; YMRS= Young Mania Rating Scale; PANSS= Positive and Negative Syndrome Scale; EQ= EuroQol

Table 3: 12 month symptom and functional outcome for SIPD and others psychosis unadjusted and adjusted for age/gender/ethnicity/DUP and baseline score

		Unadjusted				Adjusted*		
		Other Psychosis	**Substance induced psychotic disorder**	**P value**		**Other psychosis**	**Substance induced psychotic disorder**	**P value**
GAF total	N Mean score 95% CI	723 62.6 (61.3-64.0)	53 65.3 (60.3-70.3)	0.307	N Mean score 95% CI	696 62.4 (61.1-63.7)	52 63.8 (59.0-68.6)	0.595
GAF disability	N Mean score 95% CI	715 62.9 (61.7-64.2)	51 64.2 (59.5-69.0)	0.602	N Mean score 95% CI	688 62.6 (61.3-63.8)	50 63.1 (58.6-67.6)	0.821
GAF symptoms	N Mean score 95% CI	715 63.8 (62.6-65.0)	51 67.3 (62.8-71.9)	0.139	N Mean score 95% CI	688 63.6 (62.4-64.9)	50 66.6 (62.1-71.1)	0.212
PANSS total	N Mean score 95% CI	671 49.2 (48.0-50.4)	48 48.8 (44.4-53.1)	0.838	N Mean score 95% CI	591 49.1 (47.9-50.3)	45 48.9 (44.5-53.2)	0.922
PANSS positive	N Mean score 95% CI	680 11.3 (10.9-11.6)	48 11.2 (9.9-12.5)	0.947	N Mean score 95% CI	615 11.3 (11.0-11.6)	45 11.0 (9.8-12.3)	0.685
PANSS negative	N Mean score 95% CI	674 12.1 (11.7-12.5)	48 11.9 (10.3-13.4)	0.803	N Mean score 95% CI	599 12.1 (11.6-12.5)	45 12.2 (10.7-13.7)	0.832
PANSS general	N Mean score 95% CI	676 26.0 (25.4-26.6)	48 25.7 (23.4-28.0)	0.794	N Mean score 95% CI	608 25.9 (25.2-26.5)	45 25.7 (23.4-28.0)	0.887
Calgary Depression Scale	N Mean score 95% CI	688 3.5 (3.2-3.8)	46 5.0 (3.8-6.2)	**0.032**	N Mean score 95% CI	628 3.6 (3.2-3.9)	42 5.2 (3.9-6.4)	**0.015**
YMRS	N Mean score 95% CI	696 3.2 (2.8-3.6)	47 3.4 (1.9-4.8)	0.824	N Mean score 95% CI	636 3.2 (2.8-3.6)	43 3.5 (2.0-5.0)	0.743
EQ 5D total	N Mean score 95% CI	640 6.2 (6.1-6.3)	44 6.3 (5.9-6.7)	0.666	N Mean score 95% CI	613 6.3 (6.1-6.4)	43 6.2 (5.8-6.7)	0.886
EQ 5D health thermometer	N Mean score 95% CI	608 66.7 (65.0-68.4)	37 66.2 (59.5-73.0)	0.895	N Mean score 95% CI	582 67.2 (65.5-68.9)	39 66.7 (60.2-73.2)	0.890
Relapse (%) None Type 2 exacerbation Type 1 true		 561 (63.2%) 125 (14.1%) 73 (8.2%)	 35 (53.0%) 11 (16.7%) 9 (13.6%)	 0.309				 0.247
Recovery (%) None Partial Full		 91 (10.2%) 262 (29.5%) 506 (57.0%)	 7 (10.6%) 20 (30.3%) 37 (56.1%)	 0.998				 0.364

* adjusted analysis with age, gender, ethnicity, DUP (Duration of Untreated Psychosis) and baseline scores as covariates, apart from the analyses for relapse and recovery when baseline scores were not a covariate

Footnote: GAF= Global Assessment of Functioning scale; YMRS= Young Mania Rating Scale; PANSS= Positive and Negative Syndrome Scale; EQ= EuroQol